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REVIEW ARTICLE

MICROSPHERE AS DRUG CARRIER: A REVIEW

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Abstract

Development of microspheres is a promising technology for controlled release and drug targeting. Various types of microspheres such as bio-adhesive, magnetic, floating, radioactive and polymeric microspheres are developed for various purposes. Microspheres occupied a central place in novel drug delivery. There are various departments of medicine like cancer, pulmonary, cardiology, radiology, gynaecology, andoncology etc, numerous drugs are used and they are delivered by various types of drug delivery system. Among them microspheric drug delivery system has gained enormous attention due to its wide range of application as it covers targeting the drug to particular site to imaging and helping the diagnostic features. It also has advantage over various other dosage forms like we know for lungs disease now a days aerolised drugs are used for local delivery of drugs but it has disadvantage of shorter duration of action so for sustained release and reducing side effects and hence to achieve better patient compliance microspheres can be used. It also has advantage over liposomes as it is physicochemically more stable. Moreover the microspheres are of micron size so they can easily fit into various capillary beds which are also having micron size. The purpose of the review is to compile various types of microspheres, different methods to preparation, its applications and also various parameters to evaluate their efficiency.

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Introduction

The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance[1]. In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect , adverse effect decreases by lowering peak plasma concentration.[2] The controlled release dosage form maintaining relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time. One such in Microspheres as carriers of drug become an approach of controlled release dosage form in novel drug delivery system.[2] Microspheres are defined as "Monolithic sphere or therapeutic agent distributed more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level.[4] It has a particle size of (1-1000nm).3 Further, currently available slow release oral dosage forms,such as enteric coated/ double-layer tablets which release the drug for 12-24 hours still result in inefficient systemic delivery of the drug and potential gastrointestinal irritation. Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In

addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal iretention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.[4] Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.

Advantages of Microspheres[10]:

1. They facilitate accurate delivery of small quantities of potent drug and reduce concentration of drug at site other than the target organ or tissue.
2. They provide protection for unstable drug before and after administration, prior to their availability at the site of action.
3. They provide the ability to manipulate the *in vivo* action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug.
4. They enable controlled release of drug.Examples: Narcotic, Antagonist, Steroid Hormones

TYPES OF MICROSPHERES

Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.[6]The effect of different polymers on bio adhesive microspheresare given in table I.

Magnetic microspheres

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magneticresponses to a magnetic field from incorporated materials that are used for magnetic microspheresare chitosan, dextran etc.[5] The different type areTherapeutic magnetic microspheres: Are used to deliver chemotherapeutic agent to liver tumour.Drugs like proteins and peptides can also be targeted through this system.[6]

Diagnostic microspheres: Can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supramagnetic iron oxides.[7]

Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gasteric contentand increases gastricresidence and increases fluctuation in plasma concentration. Moreover it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefor ereduces dosing frequencies. Drug (ketoprofen) given through this form.[8]

Radioactive microspheres

Radio emobilisation therapy microspheres sized10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So all these condition sadcio active microspheres deliver high radiation dose to the targeted areas without damaging thenormal surrounding tissues.[9]It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microsphers are α emitters, β emitters, γ emitters.10

Polymeric microspheres

The diffent types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive in nature Biodegradable polymers prolongs the residence

time when contact with mucous membrane due to it's high degree of swelling property with aqueousmedium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer10 and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.However they provide wide range of application in microsphere based treatement.[11]

Synthetic polymeric microspheres

The interest of synthetic polymericmicrospheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe andbiocompatible.[11]But the main disadvantage of thesekind of microspheres, are tend to migrate awayfrom injection site and lead to potential risk, embolismand further organ damage.[12]

METHOD OF PREPERATION

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique.[1] The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc.[5] The various methods of preparations are

Emulsion solvent evaporation technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of pvp as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.12 Aceclofenac microspherewere prepared by this technique.

Emulsion cross linking method

In this method drug was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40 ^{0}C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 ^{o}C, results in w/o emulsion then further stirring is done for 10 min at 15 ^{0}C. Thus the produced microspheres were was respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mLof aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for crosslinking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80at 37 0 C for 10 min to block unreacted glutaraldehyde.18 Examples for this technique is Gelatin A microspheres.

Co-acervation method

Co-acervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80 ^{0}C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twicely with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.1

Co-acervation non solvent addition: Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propylisobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin 5 times with continiousstirring.1After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50oc for 4 hr.1

Spray drying technique

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefiedcoating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent.4 Organic solution of poly (epsilon-caprolactone) (PCL) andcellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may loose crystalinity due to fast drying process.[4]

Emulsion-solvent diffusion technique

In order to improve the residence time in colon floating microperticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl

sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a dessicator at room temperature. The following microperticles were sieved and collected.[4]

Multiple emulsion method

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed insolution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethylacctate. The the primary emulsion was then re emulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.4

Ionic gelation

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25 % (w/v) of diclofenac sodium was added to 1.2 % (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added dropwise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not releasein acidic pH.4

Hydroxyl appetite (HAP) microspheres in

sphere morphology

phase (Diclofenac sodium containing 5% w/w ofEVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co solvencing and helped them tostay individual droplets .While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.[19]

CHARECTERIZATION/ EVALUATION OFMICROSPHERES

Particle size analyser

Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, To prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume meandiameter in micrometer.20

Optical microscopy

This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye pieceand 45x objective) and100 particles were calculated.[21]

Scanning electron microscopy (SEM)

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slub with the help of double sided sticking tape and coated with gold film under reduced pressure.[22]

Swelling index

This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution(100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37 ^{o}C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.[23]

Entrapment efficiency

Microspheres containing of drug (5mg) were crushed and then dissolved in distilled water with the help of ultrasonic stirrer for 3 hr, and was filtered then assayed by uv-vis spectroscopy. Entrapment efficiency is equal to ratio of actual drug content to theoretical drug content[23]

X-ray diffraction

Change in crystalinity of drug can be determined by this technique. Microperticles and its individual components were analysed by the help of D & discover (Bruker, Germony).Scanning range angle between 8 0C - 70 0C.Scan speed - 4o/min Scintillation detectorPrimary silt=1mm Secondary silt=0.6 mm.1

Thermal analysis

Thermal analysis of microcapsule and its component can be done by using-Differential scanning calorimetry (DSC)Thermo gravimetric analysis (TGA)Differential thermometric analysis (DTA)Accurately the sample was weighed and heated on alumina pan at constant rate of 10oc/min under nitrogen flow of 40 ml/min.1

UV-FTTR (Fourier transform infra red)
The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.

Stability studies
By placing the microspheres in screw capped glass container and stored them at following conditions:
1. Ambient humid condition
2. Room temperature (27 ± 2^0C)
3. Oven temperature (40 ± 2^0C)
4. Refrigerator ($5\ ^0$C -8^0C).

It was carried out of a 60 days and the drug content of the microsphere was analyzed.

Zeta potential
The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W2 phase and the resulting particles were determined by zeta potential measurement.

Invitromethods[39,40,41]
There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of in vitro and in vivo techniques have been reported. In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physicochemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of in vitro release methods for buccal formulations; however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed.

Interface diffusion system
This method is developed by Dearden & Tomlinson. It consists of four compartments. The compartment A represents the oral cavity, and initially contained an appropriate concentration of drug in a buffer. The compartment B representing the buccal membrane, contained 1-octanol, and compartment C representing body fluids, contained 0.2 M HCl. The compartment D representing protein binding also contained 1-octanol. Before use, the aqueous phase and 1-octanol were saturated with each other. Samples were withdrawn and returned to compartment A with a syringe.

Dissolution apparatus
Standard USP or BP dissolution apparatus have been used to study in vitro release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.

Invivomethods[41]
Methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrate at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include invivostudies using animal models, buccal absorption tests, and perfusion chambers for studying

drug permeability.

Animal models

Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, however, very few invivo (animal). Animal models such as the dog, rats, rabbits, cat, hamster, pigs, and sheep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the oesophagus is ligated to prevent absorption pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

Buccal absorption test

The buccal absorption test was developed by Beckett & Triggs in 1967. It is a simple and reliable method for measuring the extent of drug loss of the human oral cavity for single and multicomponent mixtures of drugs. The test has been successfully used to investigate the relative importance of drug structure, contact time, initial drug concentration and pH of the solution while the drug is held in the oral cavity.

Invitro-Invivocorrelations

Correlations between in vitro dissolution rates and the rate and extent of availability as determined by blood concentration and or urinary excretion of drug or metabolites are referred to as "invitro-in vivo correlations". Such correlations allow one to develop product specifications with bioavailability.

APPLICATION

1. Microspheres in vaccine delivery[42,43]

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue. The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines49. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.

2. Targeting using microparticulate carriers[44,45]

The concept of targeting, i.e. site specific drug delivery is a well established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

3. Monoclonal antibodies mediated microspheres targeting[46]

Monoclonal antibodies targeting microspheres are immune microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The

Mabs can be attached to microspheres by any of the following methods
1. Non specific adsorption
2. Specific adsorption
3. Direct coupling
4. Coupling via reagents

4. Imaging

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintigraphic imaging of the tumour masses in lungs using labeled human serum albumin microspheres.

5. Topical porous microspheres[48,59]

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 μm. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non collapsible structures with porous surface through which active ingredients are released in a controlled manner.

6. Surface modified microspheres[50]

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns .The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:
1. Antibodies and their fragments

2. Proteins

3. Mono- oligo- and polysaccharides

4. Chelating compounds (EDTA, DTPA or Desferroxamine)

5. Synthetic soluble polymers such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body.

6. Microspheres for DNA Delivery[51,52]

Microspheres have been recently used as a delivery vehicle for the transfer of plasmid DNA which leads to improve the transfer of plasmid DNA and their stability in the bio- environment. Truong-Le & Co workers (1998) developed a novel system for gene delivery based on the use of DNA-gelatin microspheres/ nanoparticles formed by salt induced complex coacervation of gelatin & plasmid DNA as shown in table

7. Microspheres for Lymph targeting[53]

The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent the metastasis of tumor cells by accumulating the drug in the regional lymph node. Example:
Poly alkyl cyanoacrylate microspheres bearing anticancer drugs for tumor of peritoneal cavity.
Poly (lactide-co-glycolide) microspheres for the lymphatic of diagnostic agents.

Pharmaceutical Applications In Drug Delivery System

1. Ophthalmic Drug Delivery[54]

Polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, polymer hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow.

2. Gene delivery[55]

Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Polymer has been used as a carrier of DNA for gene delivery applications.

3. Oral drug delivery[56]

The potential of polymer films containing diazepam as an oral drug delivery was investigated in rabbits. The results indicated that a film composed of a 1:0.5 drug-polymer mixture might be an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of polymer to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make polymer a unique polymer for oral drug delivery applications.

4. Nasal drug delivery[57]

The nasal mucosa presents an ideal site for bioadhesive drug delivery systems. Polymer based drug delivery systems, such as micro spheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Various polymer salts such as chitosan lactate, chitosan aspartate, chitosan glutamate and chitosan hydrochloride are good candidates for nasal sustained release of vancomycin hydrochloride.

CONCLUSION

Microspheres form an important drugdelivery strategy for controlled release and targeting. Microspheres containing anti neoplasticdrugs, steroid hormones, vaccines, proteins and peptides, antiviral, antifungal andantibiotic drugs, anti-diabetic drugs and anti inflammatory drugs are investigatedextensively for controlled release by various routes and for targeting. In recent years studieson microspheres have been increased as it has become a promising technology in the areas ofdrug delivery, proteomics and genomics and also for studying bio molecular interactions.

Table 1: Summary of Recent Research on Microspheres

Sr. No	Drug/Category Polymers Used	Polymers Used	Method of Preparation	Purpose / Result	Reference
1	Cephalexin (Antibiotic)	Sodium alginate, Guargum	Ion gelation technique	Mucoadhesive polymers Guar gum in combination with sodiumalginate provides extended gastric retention and has ability to coat gastric mucosa Uniformly.	11
2	Propanolol Hydro chloride (Anti Hypertensive)	Sodium carboxy methyl	cellulose, carbopol	934p, HPMCK4M	12

3	Sitagliptin phosphate (Anti Diabetic)	Eudragit RS100,HPMC	Non aqueous solventevaporation technique	Prolonging gastric retention of the dosage form	13
4	Aceclofenac (NSAID)	EUDRAGIT S 100, EUDRAGIT L 100	Response surface methodology	Increase gastric residence of the drug	14
5	Cephalexin (Antibiotic)	Ethyl cellulose	Emulsion solvent evaporation	Prolonged drug release in the stomach at least 12 hrs	15
6	Salbutamol sulphate (Anti Asthmatic), theophylline (Anti Asthmatic)	Ethyl cellulose	Emulsion solvent evaporation	Matrix microspheres have a potential for the prolongation and simultaneous delivery of drugs	16
7	Mefenamic acid (NSAID)	Chitosan	Thermal andGlutaraldehyde cross linking	Use of chitosan to control the release of poorly water soluble drugs	17
8	Salbutamol sulphate (Broncho Dilator)	Chitosan	Spray drying method	Spray drying is useful for preparation of salbutamol sulphate loaded chitosan microspheres in presence of and absence of crosslinking agent	18
9	Aceclofenac (NSAID)	Sodium alginate	Ionic gelation Method	Decrease the dosing frequency and also prevent gastric hemarrahage	19
10	Perindopril erbumine (Anti Hypertensive)	Ethyl cellulose, HPMC, PVP K30, EUDRAGIT S 100, PVPK90	Double emulsion solvent diffusion method	Prolong the drug release in a stomach for up to 12 hrs	20
11	Losartan (Anti Hypertensive)	Ethyl cellulose, Sodium alginate, Acycoat L30D, Acycoat E 30 D	Solvent evaporation, w/o emulsion, solvent evaporation method	Solvent evaporation method gaves Maximum yield.	21
12	Losartan potassium (Anti Hypertensive)	Chitosan, Sodium alginate	Emulsification solvent evaporation method	Smoothness of the losartan potassium microspheres was increased by increasing polymer concentration	22
13	Glipizide (Anti Diabetic)	Acrycoat S100 USP, Eudragit RS100	Emulsion solvent diffusion technique	Maintain a constant drug concentration in the serum for a longer period of time	23
14	Diltiazem hydrochloride (Anti Hypertensive)	Ethyl cellulose	Emulsion solvent evaporation method	Enhance the uptake of hydrophilic substance across epithelial layer	24
15	Metformin (Anti Diabetic)	Ethylcellulose, HPMC, Carbopol 934 P, Chitosan	Non aqueous solvent evaporation method	Chitosan as a polymer exhibited maximum prolonged drug release	25

				at GIT PH or at least 15hrs	
16	Glimepiride (Anti Diabetic)	Ethyl Cellulose, Eudragit RS 100, Eudragit RL100	Emulsification solvent evaporation method	Size of the microspheres was increased with increasing concentration of polymer	26
17	Carvedilol (Anti Hypertensive)	Ethyl cellulose, PEG 6000	Spray drying	The characterization of microspheres revealed the poor flow ability of the spray dried	27
18	Nifedipine (Anti Hypertensive)	Eudragit RL 100	Solvent evaporation	Enhancing bioavailability	28
19	Nifedipine (Anti Hypertensive)	Sodium Alginate, HPMC, Carbopol	Ionic gelation method	Drug release from microspheres was found slow followed by first order kinetics with non Fickian release mechanism	29
20	Amoxicillin trihydrate	Eudragit RS 100	Solvent evaporation	Delivery of protein and peptide drugs	30
21	(AntRitonovir (Anti Viral)ibiotic)	Mixture of sodium alginate and HPMC	Ionic gelation method	Increase the gastric retention time of drug	31
22	Indomethacin (NSAID)	Ethyl cellulose N 10, Ethyl cellulose N 100	Emulsion solvent evaporation	Ethylcellulose N10 and N100 membrane materials indicated differences in release patterns of microspheres. Microspheres exhibited lower burst effect with ethyl cellulose N100	32
23	Metformin hydrochloride (Anti Diabetic)	Sodium Carboxy Methyl Cellulose, Carbopol 934P, HPMC K 4M	Emulsion solvent evaporation	Reduce the dosing frequency and improving patient compliance by designing sustained release Mucoadhesive microspheres	33
24	Ascorbic acid	(Anti Oxidant)	Ethyl cellulose coacervation technique	Derived properties of ascorbic acid loaded microspheres, the prepared product has uniform size and shape, spherical in particle size and passable flow property	34
25	Metformin Hcl (Anti Diabetic)	Eudragit RL 100, cellulose acetate butyrate	w/o emulsion solvent evaporation method	Drug loaded floating microspheres will overcome the drawbacks associated with drug in conventional tablet form reducing plasma drug conc. fluctuations	35

26	Lamivudine (Anti Viral)	Acryl coat L 30D and S 100	Solvent evaporation method	Plasma concentration was maintained above the minimum effective concentration for longer time after administration of microspheres	36
27	Melaxicam (Anti Inflammatory)	Polyvinyl Alcohol, PEG 6000, Gelatin	Emulsion solvent evaporation method	Emulsion solvent evaporation method is suitable for encapsulating lipophilic drugs.	37
28	Glipizide (Anti Diabetic)	Ethyl Cellulose, HPMC, Methocel K 100 M CR	Solvent evaporation method	Use of this approach has the potential not only to improve the Therapeutic effectiveness of the drug but also to allow a reduction in the total drug needed	38

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